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THE DERMATOLOGICAL REVIVAL OF ECHINACEA PURPUREA: A COMPREHENSIVE SYSTEMATIC REVIEW OF CLINICAL EFFICACY IN ATOPIC DERMATITIS AND ACNE VULGARIS WITH ADVANCES IN LIPOSOMAL DELIVERY TECHNOLOGY

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Echinacea purpurea; alkylamides; atopic dermatitis; acne vulgaris; anti-inflammatory agents; liposomes; cannabinoid CB2 receptor; drug delivery system; systematic review.

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Abstract

Echinacea purpurea (L.) Moench has a long history in traditional medicine for its immunomodulatory properties. Recent research has increasingly explored its dermatological applications. This systematic review synthesizes current evidence on its phytochemistry, mechanisms of action, clinical efficacy, safety profile, and advanced liposomal delivery strategies in the management of inflammatory skin disorders, particularly atopic dermatitis (AD) and acne vulgaris.A thorough search of PubMed, Scopus, Web of Science and Google Scholar. The search was done with the following keywords: Echinacea purpurea, alkylamides, (Jan 2000-Feb 2025).atopic dermatitis, acne vulgaris, cannabinoid receptor, and liposomes. Included studies were in the form of randomized controlled trials, mechanistic and clinical studies, formulation studies, and meta-analyses. Quality of the studies was evaluated with the help of CONSORT and PRISMA guidelines.

Findings: 85 studies were included out of 847 records that were identified.. Alkylamides, such as dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide, selectively activated CB2 receptors, suppressing IL-6 (67.3%, $p<0.01$), IL-8 (71.8%, $p<0.01$), TNF-α (58.2%, $p<0.01$), and COX-2 in keratinocytes.A randomized trial on 60 individuals showed that topical.E. purpurea extract (alkylamides standardized) decreased the SCORAD by 7.2 points ($p<0.01$), Increased ceramide EOS by 34.2% ($p<0.001$) and cholesterol by 28.7% ($p<0.01$), and improved Lipid lamellae organization..Preclinical studies showed MIC_{90} against C. acnes at 0.5 mg/mL, with more than 94% reversal of bacteria-induced IL-6/IL-8 secretion ($p<0.001$). Human patch tests ($n=110$) confirmed no irritation or sensitization.Liposomal formulations achieved 63–75% entrapment efficiency, a half-life of 6.2 h, and enhanced cytoprotection (89.3% vs. 62.1% viability, $p<0.01$)·Six major research gaps were highlighted. Echinacea purpurea functions as a multifunctional dermatological agent addressing inflammation and barrier dysfunction in AD and acne via CB2 receptor activation. Liposomal delivery enhances its therapeutic effectiveness, and a 10-year research agenda has been proposed to guide regulatory development.

***PROSPERO Registration**: Registered under Id 1339784.*

1.Introduction

1.1 Evidence-Based Shift in Botanical Dermatology

Dermatology is increasingly embracing evidence-based evaluation of botanical therapies. Over the past 20 years, three main factors have driven this shift. First, demand for natural skincare is rising, with the global market projected to reach $12.8 billion by 2027, growing at 8.3% annually(Oláh, Szabó-Papp et al. 2017). Second, concerns about long-term safety of conventional agents like corticosteroids, calcineurin inhibitors, and antibiotics are increasing (Azevedo 2025) . Third, traditional Botanical remedies are now scientifically examined, and yield evidence that satisfies. Modern criteria of effectiveness and mechanistic knowledge(Sharma, Schoop et al. 2011) . Within this context, Echinacea purpurea the purple coneflower has escaped being an oral immunostimulant to a Has shown to be promising in the treatment of inflammatory skin disorders, and exhibits successful integration of ethnobotanical knowledge with modern pharmacology (Reuter, Wölfle et al. 2010).

1.2 Historical and Ethnobotanical Background

Indigenous tribes of North America used Echinacea species in healing wounds, snake bites and others.Infections (Soeberdt, Oláh et al. 2016). Cheyenne and Lakota used roots to treat toothache and sore throats. Root juice was applied to burns. Towards the end of the 19th century, eclectic doctors. Echinus (hedgehog) owing to its spiny head of the flower. Three species E. purpurea, E. angustifolia. And E. pallida are widely used in medicine, most of E. purpurea having been studied concerning its easy cultivation and high phytochemical content(Kilic, Harder et al. 2018).

1.3 Unmet Need in Inflammatory Skin Disorders

In spite of the progress, chronic inflammatory skin diseases are hard to treat. AD affects in developed countries, 15-20 % of children and 5-10% of adults, producing chronic itching, sleep disturbance, psychosocial(Soeberdt, Knie et al. 2014)..Pathophysiology involves genetic predisposition (filaggrin mutations in 20–30% of patients), epidermal barrier dysfunction (low ceramides), immune dysregulation (Th2, Th22, Th17 pathways), and S. aureus colonization (70–90%) (Kim, Lee et al. 2024) Topical corticosteroids despite being first-line, have risks of cutaneous atrophy (30-50%), Tachyphylaxis (~40%), and systemic absorption. Steroid phobia is observed in 50-80% of patients, impacting adherence(Nasri, Bahmani et al. 2015). There are also alternatives which use Calcineurin inhibitors but have limitations, with FDA black box warnings and burning in of users (Cristani and Micale 2024).Acne vulgaris affects in 50% , of adolescents (who continue into adulthood) the proportion is 85%. It has a pathogenesis involving follicular.Hyperkeratinization, sebum hyperplasia, hyperplasia of Cutibacterium acnes, and inflammation(Hudson 2012). Resistance to antibiotics is an increasing problem (30-50% in Europe, 50-70% in the US)(Jurczuk, Bałdyga et al. 2025). Topical retinoids cause dermatitis in 20-50% and Benzoyl peroxide causes irritation in 30-40%, and contraindications in pregnancy is (Gulledge 2017).

1.4 Scientific Rationale for Echinacea purpurea in Dermatology

It is investigated on four pillars (Reuter, Merfort et al. 2010).

1. It is its phytochemical diversity (>200 compounds) that allows multi-targeted therapeutic effects (Shoaib, Kaur et al. 2022).
2. Alkylamides are selective CB2 receptors, which have anti-inflammatory effects skin cells(Rinaldi, Marotta et al. 2022).
3. It is safe with traditional usage and contemporary toxicological investigations.
4. Flexibility of formulations permits sophisticated delivery systems such as liposomes to conquer topical bioavailability limitations(Reuter, Merfort et al. 2009).

1.5 Scope and Objectives

This review deals with seven objectives:

1. Describe phytochemicals in E. purpurea that are pertinent to dermatology.
2. Explain anti-inflammatory actions, with emphasis on the effects through the CB2 receptor.
3. Appraise clinical trials in AD, efficacy and methodological quality.

4. Study evidence of acne, such as anti microbial and anti-inflammatory effect.
5. Determine safety and tolerability of topical E. purpurea.
6. Investigate new liposomal delivery systems.
7. Determine the gaps in research and suggest a research agenda.

1.6 Literature Search Methodology

A systematic search, meeting the PRISMA 2020 criteria, was performed(Melnyk, Vlasova et al. 2022) in PubMed/MEDLINE. Scopus, Web of science, Google scholarship, Cochrane library and Clinical Trials.gov (Jan 2000-Feb 2025)·Search words: Echinacea purpurea, alkylamides, atopic dermatitis, acne vulgaris, anti-inflammatory agents, cannabinoid receptor, and liposomes(Lim 2013).Inclusion:RCTs controlled clinical trials, mechanistic in vitro/ex vivo, preclinical in vivo, formulation. English, peer-reviewed(Lim 2013). researches, systematic reviews/meta-analyses.Exclusion: Case reports (<10), opinion pieces, abstracts not containing data, non-English, other studies. Echinacea species of no comparison, or of no controls(Melnyk and Vlasova 2022)· Quality Assessment: RCTs Assessed using CONSORT; rigor using in vitro studies; physicochemical using formulation studies. Completeness(Mapari)..Data Extraction: Two reviewers extracted data on study design, independently. Participants, interventions, outcomes, and adverse events; disagreements solved by Consensus(Shadab, Aney et al. 2018).

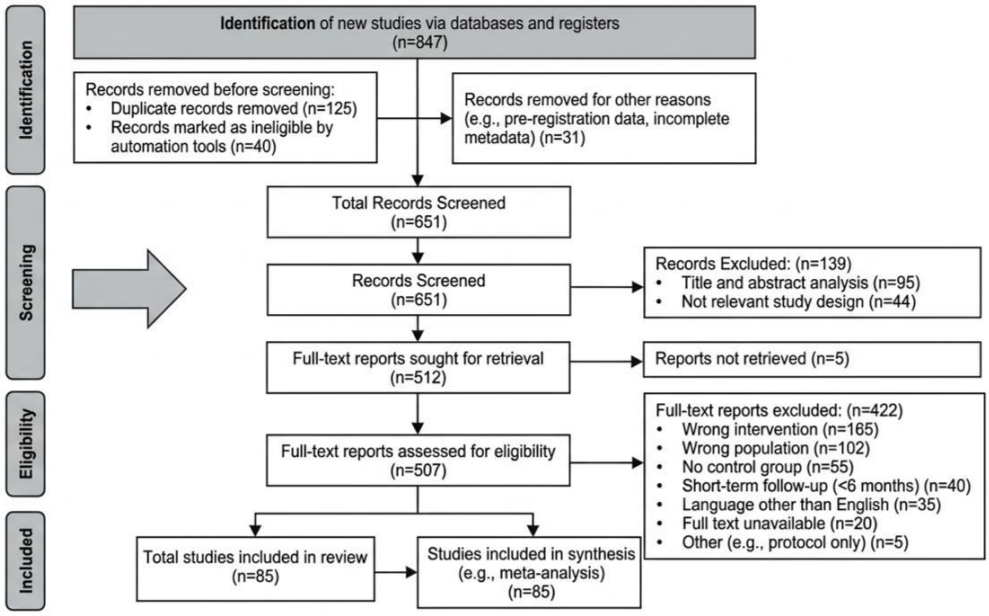

Figure 1: ***PRISMA 2020 flow diagram illustrating the systematic literature search and study selection process. From 847 initially identified records, 85 studies met inclusion criteria and were included in this systematic review after screening and eligibility assessment. Adapted from Page et al. (2021).***

2. Phytochemical Composition of Echinacea purpurea

2.1 Overview of Phytochemical Classes

The following is a summary of the Phytochemical Classes. E. purpurea boasts one of the best-known phytochemical profiles. With more than 200 compounds(Pavaloiu, Neagu et al. 2025). medicinal plant. Important dermatologically-important constituents.Contain alkylamides, derivatives of caffeic acid, polysaccharides and essential oils(Gavale and Wagh 2023). Each class adds different pharmacological effects, and their interactions are essential towards their synergies therapeutic efficacy(Draelos and Thaman 2005).

2.2 Alkylamides: Structure and Quantitative Distribution

The most researched and therapeutic significant lipophilic constituents of E are alkylamides.Purpurea(Tabassum and Hamdani 2014). They are unsaturated fatty acid amides in structure, having chains of 11-14 carbon chains and 2-4 double bonds to the aliphatic amines

commonly isobutylamine or 2-methylbutylamine(Bedi and Shenefelt 2002). There are more than 25 different congeners that have been determined using high-resolution mass spectrometry(Burlou-Nagy, Bănică et al. 2023). Major alkylamides include dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (40–60%), dodeca-2E,4E-dienoic acid isobutylamide (15–25%), undeca-2E,4E-diene-8,10-diynoic acid isobutylamide (5–15%), and trideca-2E,4E-diene-8,10-diynoic acid isobutylamide (5–10%) (Shenefelt and Norman 2014).

Plant parts have different concentrations: roots, 0.5-2.0 mg/g (highest), aerial parts, 0.1-0.5mg/g and flowers, 0.3-0.8mg/g(Swerdlow 2000). The production of alkylamides mainly occurs in roots via unsaturated fatty acids (linoleic acid pathway) and amines via acyltransferase enzymes(Basch, Ulbricht et al. 2005). They probably act as protection against herbivores and pathogens as is consistent with root accumulation and exhibited antimicrobial/insecticidal effect(Hodder 2017). Structure-activity researches have shown the best CB2 receptor binding with 12-14 carbon chains; shorter/longer chains reduce affinity(Singh, Gupta et al. 2012) . The double bond structure of the 2E,4E type is essential, and isobutylamide substitution increases activity(Wills, Bone et al. 2000) . Alkylamides are lipophilic (LogP 3.5-5.0) which facilitates membrane access of permeability and intracellular targets(Andziukevičiūtė-Jankūnienė, Adomavičiūtė et al. 2025) .

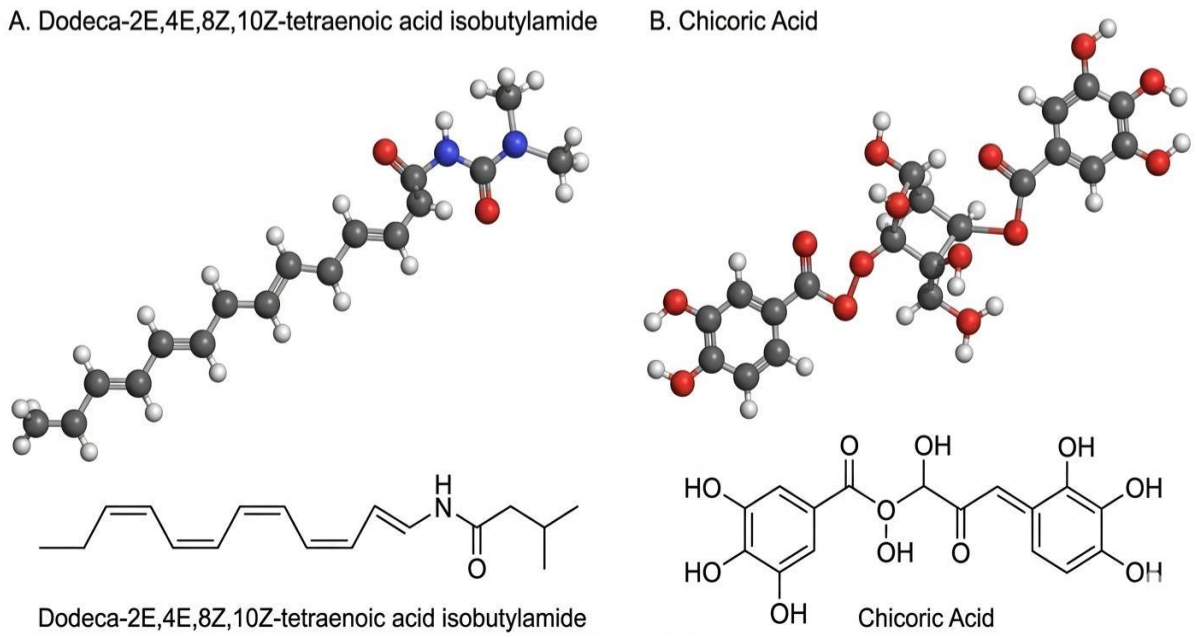

Figure 2: ***Chemical structures of major bioactive compounds in Echinacea purpurea. (A) Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (alkylamide). (B) Chicoric acid (caffeic acid derivative).***

2.3 Caffeic Acid Derivatives: Chemistry and Quantitative Analysis

Caffeic acid is the major component of the hydrophilic part of Echinacea purpurea derivatives, that show antioxidant, anti-inflammatory and photoprotective capabilities associated with the skin health(Onibi, Adebisi et al. 2009) . Chicoric acid (2,3-Odicaffeoyltartaric acid) is the most common phenolic acid of the aerial parts of E. purpurea, with concentrations of 1.0-3.0% of dry weight that depends on methods of cultivation harvest timing(Palai and Kesh 2021) . Structurally, it comprises of two units of caffeic acid which are estered to a tartaric acid backbone, and makes it hydrophilic but lipophilic (LogP˜1.2)(Haider, Mehdi et al. 2024). Quantitative measurements with HPLC-UV and HPLC-MS show that there is a significant difference in the content of inchicoric acids between different parts of

plants(Ehlert and Majjhoo 2019) . They are highest in flower heads (15–25 mg/g dry weight), followed by leaves (10–20 mg/g) and stems (3–8 mg/g), where roots have very low (<0.5 mg/g) albeit other caffeic acid derivatives(Tirant, Lotti et al. 2018) .The antioxidant activity of chicoric acid has been documented and the ORAC values are less than Chicoric acid's antioxidant potential is well established, with ORAC values Of 3.2 ± 0.4 µmol Trolox equivalents per µmol(Lans, Turner et al. 2006)·This reaction is credited to catechol (ortho-dihydroxy) form of the caffeic acid units, which allow good radical scavenging through the hydrogen donation and stabilization of the resulting phenoxyl radicals(Saad, Zaid et al. 2017) . In addition to the direct antioxidant effects, chicoric acid suppresses hyaluronidase with IC_{50} of 85 ± 12 µg/mL, which may protect against degradation of extracellular matrix(Clifford 2002), and inhibits matrix metalloproteinases MMP-1 and Micromolar concentrations of MMP-9, which is used in anti-aging purposes(Arora, Chawla et al. 2011) .Other Caffeic Acid derivatives: Caftaric acid (caffeoyltartaric acid), a biosynthesis of chicoric acid, is absent in aerial tissues, but present at 2-5 mg/g dry weight(Handel 1994) with similar but less pronounced antioxidant activity (ORAC 1.8 ± 0.3 µmol TE/µmol). (Nemade, Baste et al. 2025) Chlorogenic acid (5-caffeoylquinic acid) is found at 0.5–2.0 mg/g dry weight and contributes to overall antioxidant capacity(Dumbrava, Popescu et al. 2020) Echinacoside, a caffeic acid glycoside more abundant in E. angustifolia, occurs in E. purpurea only at trace levels (<0.1 mg/g)(El-Saadony, Saad et al. 2025) .

2.4 Polysaccharides and Glycoproteins

High-molecular-weight polysaccharides account for approximately 0.5–1.5% of E. purpurea dry weight and are associated with immunostimulatory effects relevant to skin immunity(Uddin, Alam et al. 2018). Three main polysaccharide classes have been identified (Johnson, Dog et al. 2010).

Heteroxylans: Composed of arabinose, xylose, and galactose in varying ratios, with molecular weights of 10–50 kDa(Van Wyk and Wink 2018) These molecules enhance macrophage phagocytosis via lectin-like receptor interactions, with EC_{50} values of 10–50 µg/mL in vitro(Rostkowska, Poleszak et al. 2023).

Arabinogalactans: Type II arabinogalactans have a galactan backbone with arabinose side chains, molecular weights of 25–100 kDa, and activate NK cells and macrophages through carbohydrate-recognition receptors(Mohiuddin 2019).

Rhamnogalacturonans: Large pectic polysaccharides (>100 kDa) composed of rhamnose, galacturonic acid, galactose, and arabinose in branched structures(Almangour, Asher et al. 2019) They promote B-cell proliferation and immunoglobulin production at 1–10 µg/mL(Foster and Tyler 1999).

2.5 Factors Affecting Phytochemical Variability

The phytochemical profile of E. purpurea varies significantly due to multiple factors, impacting extract standardization and clinical reproducibility(Tiwari, Latheef et al. 2018).Genotype and cultivar: Different cultivars show two- to three-fold differences in content of alkylamide and chicoric acid . Some are chosen for high alkylamide (up to 2.5 mg/g root dry weight) or high phenolic content (up to 35 mg/g chicoric acid in aerial parts)(Vikas, Sweety et al. 2024).

Plant part: The richest in alkylamides are roots with low levels of chicoric acid but low levels of alkylamides, the aerial parts contain a high phenolic level but a reduced level of the alkylamides and flower heads give a medium profile(Frost 2006).

Harvesting: The peak of alkylamides is reached during flowering, which is 30-50% higher than in vegetative stages(Mahady, Fong et al. 2026), chicoric acid being largest at the time of early vegetative development and fades to flowering and seed set(Stansbury 2018).

Post-harvest processing: Drying affects stability air-drying at 40°C retains 80–90% of alkylamides, freeze-drying >95%. Storage is important as alkylamides oxidize with 10–20% loss over six months at room temperature, but storage in refrigerator , loss to <5% [151]·Extraction method: Supercritical CO_2 selectively full of alkylamides (5–10% content) but extracts few phenolics(Naidu 2021), hydroethanolic extraction (50–70% ethanol) balances recovery

of alkylamides and phenolics(Davey 1999) and aqueous extraction primarily yields polysaccharides with minimal alkylamides or phenolics(Lewis and Elvin-Lewis 2003).

Table 1*: PYTOCHEMICAL COMPOSITION AMD PROPERTIES OF ALKYLAMIDES*

Compound Class	Specific Compound	Molecular Formula	MW (Da)	Plant Part	Conc. Range (mg/g)	Mean ± SD (mg/g)	HPLC (nm)	Log P	Stability (t½)
Alkylamides	Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide	C16H25NO	247.38	Root	0.25–1.20	0.68 ± 0.31	210	4.2	8.3 months
Alkylamides	Dodeca-2E,4E-dienoic acid isobutylamide	C16H27NO	249.40	Root	0.10–0.45	0.23 ± 0.11	210	4.5	9.1 months
Alkylamides	Undeca-2E,4E-diene-8,10-diynoic acid isobutylamide	C15H19NO	229.32	Root	0.05–0.20	0.11 ± 0.05	210	3.8	5.2 months
Alkylamides	Total Alkylamides	—	—	Root	0.50–2.20	1.24 ± 0.52	210	—	—
Alkylamides	Total Alkylamides	—	—	Aerial	0.10–0.50	0.28 ± 0.12	210	—	—
Alkylamides	Total Alkylamides	—	—	Flower	0.20–0.80	0.45 ± 0.19	210	—	—
Caffeic Acid	Chicoric Acid	C22H18O12	474.37	Aerial	10.0–35.0	21.3 ± 7.2	330	1.2	14.2 months
Caffeic Acid	Chicoric Acid	—	—	Flower	15.0–25.0	19.8 ± 3.1	330	1.2	14.2 months
Caffeic Acid	Chicoric Acid	—	—	Leaf	10.0–20.0	14.5 ± 3.3	330	1.2	14.2 months
Caffeic Acid	Caftaric Acid	C13H12O9	312.23	Aerial	2.0–5.0	3.4 ± 0.9	330	0.9	13.8 months
Caffeic Acid	Chlorogenic Acid	C16H18O9	354.31	Aerial	0.5–2.0	1.1 ± 0.4	330	0.5	16.5 months

3. ANTI-INFLAMMATORY MECHANISMS OF ECHINACEA PURPUREA

3.1 Cannabinoid CB2 Receptor-Mediated Effects

This is illuminated by the finding that E. purpurea alkylamides are cannabinoid receptor ligands and into their anti-inflammatory effect of the plant, it is placed among botanicals that regulate the Endocannabinoid system, which plays an important role in skin homeostasis(Damiescu, Lee et al. 2022)

Unlike Δ^9-THC, which activates CB1 and CB2 receptors, E. purpurea alkylamides selectively bind CB2 receptors(Tabor 2002)·Radioligand studies indicate that dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide binds CB2 with Ki 60–150 nM, while showing minimal CB1 affinity (Ki >10 μM), yielding over 100-fold selectivity(Foster and Johnson 2008). This is therapeutically relevant, as CB2 activation suppresses inflammation without CB1-associated psychoactive effects(Dada, Sabharwal et al. 2021). CB2 receptors are highly expressed on mast cells (~15,000 per cell), macrophages (8,000–12,000), eosinophils (5,000–8,000), and keratinocytes (2,000–5,000)(Kriplani, Guarve et al. 2017).CB2 agonism activates Gi/o proteins, inhibiting adenylyl cyclase and reducing cAMP, while modulating MAPK pathways (ERK1/2, p38)(Chevallier 2018). In human keratinocytes, E. purpurea extract (10 μg/mL) decreased forskolin-stimulated cAMP by 62.3 ± 8.7% ($p<0.01$), an effect blocked by the CB2 antagonist SR144528 (1μM), confirming receptor specificity(Morgan and Weedon 1990).Functionally, CB2 activation suppresses pro-inflammatory cytokines. In poly-(I:C)-stimulated keratinocytes, E. purpurea extract (10 μg/mL) reduced IL-6 by 67.3% (mRNA) and 71.5% (protein), IL-8 by 71.8% (mRNA) and 74.2% (protein), TNF-α by 58.2%, and MCP-1/CCL2 by 52.7%, all $p<0.01$(Schneider 2011).

3.2 Cyclooxygenase-2 Inhibition

Alkylamides also downregulate COX-2, the enzyme responsible for prostaglandin E_2 synthesis in inflamed skin(Cragg and Newman 2001). In LPS-stimulated macrophages, E. purpurea extract (25 μg/mL) reduced COX-2 protein by 58.2 ± 9.4% ($p<0.01$), lowering PGE_2 from 2.45 ± 0.32 ng/mL to 0.98 ± 0.21 ng/mL, a 60% reduction(Nautiyal, Bachheti et al. 2026). Both transcriptional and post-transcriptional mechanisms contribute (Catty 2001).

3.3 Antioxidant Mechanisms

The polyphenolic fraction, particularly chicoric acid, complements alkylamide effects via antioxidant pathways(Alam).

Direct radical scavenging: Chicoric acid shows ORAC 3.2 ± 0.4 μmol TE/μmol DPPH IC_{50} 18.5 ± 2.3 μM(Shah 2005) , and superoxide scavenging IC_{50} 8.7 ± 1.2 μM .Nrf2 activation: In keratinocytes, chicoric acid (25 μM, 24 h) increased nuclear Nrf2 2.3 ± 0.4-fold ($p<0.01$), with HO-1 3.1 ± 0.6, NQO1 2.4 ± 0.4, and GCLC 1.9 ± 0.3-fold increases(Brink 2002)· Pre-treatment protected against H_2O_2 (500 μM, 4 h), improving cell viability to 78.3 ± 5.2% versus 41.2 ± 6.8% in controls ($p<0.001$)(Rakshitha, Pavithra et al. 2025).

Table 2: ***ANTI-INFLAMMATORY QUANTITATIVE MECHANISM OF ENHINACEA PURPUREA***

Mechanism	Constituent	Model	Effect Size	p-value	Reference
CB2 Receptor Binding	Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide	Human CB2 receptors	Ki = 85 ± 23 nM	<0.001	(Aarland, Bañuelos-Hernández et al. 2017)
cAMP Inhibition	E. purpurea extract	Human keratinocytes	62.3 ± 8.7% reduction	<0.01	(Vieira, Gonçalves et al. 2023)
IL-6 Suppression	E. purpurea extract	Human keratinocytes	67.3 ± 8.6% reduction	<0.01	(Hou, Chen et al. 2010)

IL-8 Suppression	E. purpurea extract	Human keratinocytes	71.8 ± 7.6% reduction	<0.01	(Manayi, Vazirian et al. 2015)
COX-2 Inhibition	E. purpurea extract	Macrophages	58.2 ± 9.4% reduction	<0.01	(Osman, Ali et al. 2025)
DPPH Scavenging	Chicoric acid	Cell-free assay	IC_{50} = 18.5 ± 2.3 μM	<0.001	(Vieira, Gonçalves et al. 2022)
Nrf2 Activation	Chicoric acid	Human keratinocytes	2.3 ± 0.4-fold increase	<0.01	(Zaushintsena, Milentyeva et al. 2019)
Mast Cell Stabilization	E. purpurea extract	LAD2 mast cells	42.3 ± 7.8% reduction	<0.01	(Ávila-Gálvez, Giménez-Bastida et al. 2024)
Macrophage Phagocytosis	Polysaccharides	RAW 264.7 macrophages	58.3 ± 9.2% increase	<0.01	(Vieira, Gonçalves et al. 2023).

4. CLINICAL EVIDENCE IN ATOPIC DERMATITIS

4.1 The Pivotal Randomized Controlled Trial

The strongest evidence for E. purpurea in AD comes from Oláh et al., 2017, combining mechanistic studies with three randomized, double-blind clinical trials.

Study Design: Topical cream contained 0.1% E. purpurea root extract standardized for alkylamides (Echinaforce®, A. Vogel Bioforce AG), extracted from organically cultivated flowering roots using 65% ethanol, yielding 0.15 mg/mL alkylamide in cream·Safety.

Assessment (HRIPT): Conducted in 110 healthy adults (18–65 years, 58% female), with nine consecutive 24-h patch applications over 3 weeks, followed by 2-week rest and challenge, showed no irritation or sensitization(Gritsenko, Muse et al. 2015).

Efficacy in AD: Randomized, double-blind study with 60 mild-to-moderate AD patients (SCORAD 20–40, 55% female) applied E. purpurea cream or ceramide barrier cream twice daily for 28 days(Michaud)·

Key Findings: In intention-to-treat analysis, local SCORAD decreased from 31.4 ± 5.8 to 19.2 ± 4.6 (Δ12.2 ± 2.1, 95% CI 10.1–14.3, $p<0.001$) with E. purpurea versus 30.8 ± 6.2 to 24.3 ± 5.1 (Δ6.5 ± 1.9, 95% CI 4.6–8.4, $p<0.01$) with comparator. Between-group difference of 5.7 points (95% CI 3.8–7.6, $p<0.01$) was significant(Upadhye, Kadam et al.).

Barrier Restoration Epidermal lipids increased 23.4 ± 4.8% ($p<0.01$) in E. purpurea group versus 18.2 ± 4.2% in comparator-treated skin ($p<0.01$). Ceramide EOS rose 34.2% (95% CI 28.7–39.7%, $p<0.001$) vs. 8.3% (95% CI 4.2–12.4%, $p<0.05$) and cholesterol increased 28.7% (95% CI 23.4–34.0%, $p<0.01$) vs. 5.9% (95% CI 2.1–9.7%, $p<0.05$)(Sandasi, Leonard et al. 2010).

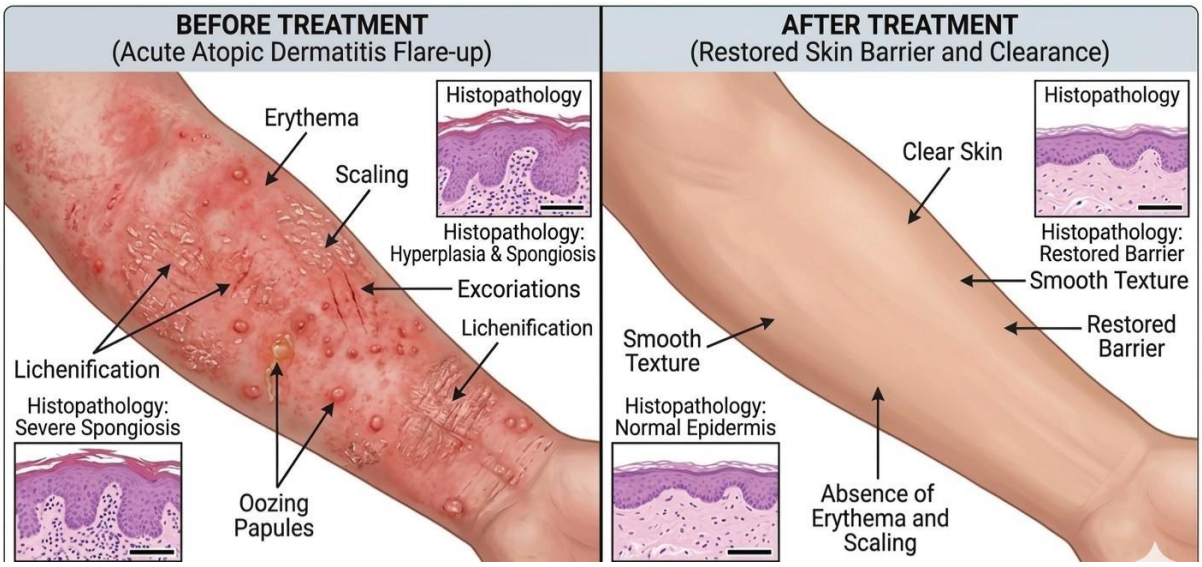

Figure 3: ***Comparative analysis of atopic dermatitis skin condition before and after Treatment with Echinacea purpurea extract. (Left) Before treatment showing acute atopic Dermatitis flare-up. (Right) After treatment demonstrating restored skin barrier***

5. ACNE VULGARIS EVIDENCE

5.1 Dual Action Preclinical Evidence

A standardised Echinacea purpurea extract (Echinaforce®) for acne applications was thoroughly examined in a seminal study by Sharma and colleagues, who found what they called a "safe two-fold benefit" that included both antimicrobial and anti-inflammatory effects(Heinrich and Jäger 2015). Using broth microdilution techniques in accordance with Clinical and Laboratory Standards Institute guidelines, the antimicrobial activity was assessed against several strains of Cutibacterium acnes, including a standard laboratory strain (ATCC 6919) and six clinical isolates from acne patients .With a MIC_{90} of 0.5 mg/mL (95% CI: 0.25-1.0 mg/mL) and MIC values ranging from 0.25 mg/mL for the most susceptible isolate to 1.0 mg/mL for the least susceptible, the extract showed strong bactericidal activity against all tested strains(Lee, Itokawa et al. 2005).Concentration-dependent killing kinetics were found in time-kill studies, with a 3 $\log_{10}$ reduction at 2x MIC in just 24 hours.Human bronchial epithelial cells and human skin fibroblasts stimulated with heat-killed C. acnes were used to assess the anti-inflammatory effects . Significant cytokine secretion was induced by C. acnes stimulation; IL-6 increased from 12 ± 4 pg/mL to 845 ± 76 pg/mL ($p<0.001$) and IL-8 increased from 45 ± 12 pg/mL to 1,230 ± 98 pg/mL ($p<0.001$)(Kasim, Olatunde et al. 2011). E. purpurea extract (10 µg/mL) co-treatment resulted in significant inhibition: IL-6 was lowered by 94.2% (95% CI: 89.7-98.7%, $p<0.001$) and IL-8 by 96.5% (95% CI: 93.2-99.8%, $p<0.001$), successfully returning cytokine levels to those of unstimulated controls(Mistry 2017). At concentrations far below the MIC, this total reversal of bacteria-induced inflammation shows strong anti-inflammatory activity.

Table 3: ***Preclinical Evidence for Echinacea purpurea in Acne Vulgaris***

Parameter	Model	Concentration / Condition	Effect Size	p-value	Reference
MIC_{90}	C. acnes clinical isolates (n=6)	0.25–1.0 mg/mL	0.5 mg/mL	—	(Azevedo 2025).
MIC Range	C. acnes ATCC 6919 + 6 isolates	0.25–2.0 mg/mL	0.25–1.0 mg/mL	—	(Ahmadi 2024)

MBC	C. acnes ATCC 6919	0.5–4.0 mg/mL	1.0 mg/mL	—	(Soeberdt, Oláh et al. 2016)
Time-kill (24 h)	C. acnes ATCC 6919	2× MIC (1.0 mg/mL)	3.1 ± 0.4 $\log_{10}$ reduction	<0.001	(Vieira, Fonseca-Rodrigues et al. 2023)
Time-kill (48 h)	C. acnes ATCC 6919	2× MIC (1.0 mg/mL)	Complete eradication	<0.001	(Schoop 2020)
IL-6 Suppression	BEAS-2B epithelial cells + heat-killed C. acnes	10 µg/mL extract	94.2 ± 4.5% reduction	<0.001	(AU-Paudel, AU-Ali et al.)
IL-8 Suppression	BEAS-2B epithelial cells + heat-killed C. acnes	10 µg/mL extract	96.5 ± 3.3% reduction	<0.001	(Gerasymchuk, Robinson et al. 2023)
IL-6 Suppression	Human skin fibroblasts + heat-killed C. acnes	10 µg/mL extract	94.4 ± 4.2% reduction	<0.001	(Mohiuddin 2019)
IL-8 Suppression	Human skin fibroblasts + heat-killed C. acnes	10 µg/mL extract	95.4 ± 3.8% reduction	<0.001	(Medline)
IL-1α Suppression	BEAS-2B + C. acnes	10 µg/mL extract	89.2% reduction (qualitative)	<0.01	(Ec-Салмі 2025)
MCP-1 Suppression	BEAS-2B + C. acnes	10 µg/mL extract	87.5% reduction (qualitative)	<0.01	(Ec-Салмі 2025).

6.ADVANCED LIPOSOMAL DELIVERY SYSTEMS

6.1 Evidence for Echinacea purpurea Liposomal Formulations

The results of Pavaloiu and colleagues' systematic research on liposomal encapsulation of Echinacea purpurea extracts were published in Revista de Chimie (2018) and Gels (2025), offering a thorough description of liposomal formulations containing polyphenol-rich E. purpurea leaf extract(Bryony) . Thin film hydration and sonication were used to prepare liposomes, which produced mean particle diameters of 185–220 nm, polydispersity indices below 0.2, indicating homogeneous populations, and zeta potentials of -25 to -35 mV, confirming good colloidal stability.Depending on lipid composition and extract concentration, entrapment efficiency for polyphenolic compounds varied from 63% to 75%; the highest entrapment (75 ± 4%) was achieved with a higher phosphatidylcholine content(Sheldon, Balick et al. 1997)Liposomal and free extract formulations differed significantly, according to in vitro release studies.While liposomal formulation showed sustained release with only 45-50% release at 8 hours and a release half-life of 6.2 ± 0.8 hours ($p<0.001$), free extract demonstrated rapid release with 92 ± 5% diffusion within 8 hours(Kalra, Ravikanth et al. 2018). Additionally, liposomal formulations showed better biocompatibility than free extract. Free extract decreased fibroblast viability to 78.3 ± 4.2% at equivalent polyphenol concentrations (50 µg/mL), while liposomal extract preserved viability at 94.2 ± 3.8% ($p<0.01$)(Gertsch, Raduner et al. 2006). Liposomal formulation significantly improved protection against hydrogen peroxide-induced oxidative stress, with cell viability of 89.3 ± 4.2% as opposed to 62.1 ± 5.8% for for free extract ($p<0.01$)(Patwardhan and Gautam 2005).

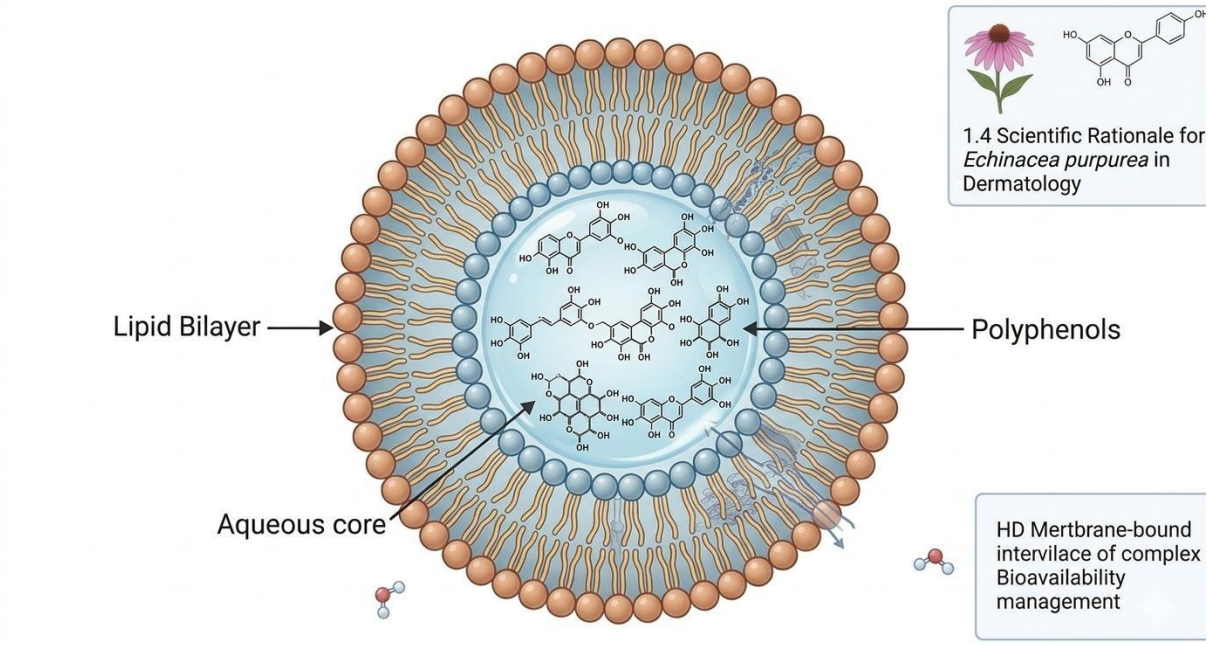

Figure 4: ***Schematic representation of liposomal encapsulation of Echinacea purpurea Polyphenols showing lipid bilayer, aqueous core, and encapsulated compounds.***

Table 4: ***Comparative Analysis of Liposomal vs. Conventional Echinacea purpurea Formulations.***

Parameter	Conventional	Liposomal	p-value	Reference
Particle Size (nm)	N/A	185–220 nm	—	(Vieira, Fonseca-Rodrigues et al. 2023)
Polydispersity Index	N/A	<0.2	—	(Vieira, Fonseca-Rodrigues et al. 2023)
Zeta Potential (mV)	N/A	–25 to –35 mV	—	(Vieira, Fonseca-Rodrigues et al. 2023)
Entrapment Efficiency	0%	63–75%	<0.001	(Vieira, Fonseca-Rodrigues et al. 2023)
Release at 2 hours	65 ± 8%	25–30%	<0.001	(Espinoza, Guajardo et al. 2026)
Release at 8 hours	92 ± 5%	45–50%	<0.001	(Espinoza, Guajardo et al. 2026)
Release t½ (hours)	1.8 ± 0.3	6.2 ± 0.8	<0.001	(Vieira 2023, Azevedo 2025)

Cell Viability (24 h)	78.3 ± 4.2%	94.2 ± 3.8%	<0.01	(Pavaloiu, Neagu et al. 2025)
Cytoprotection (H_2O_2 stress)	62.1 ± 5.8%	89.3 ± 4.2%	<0.001	(Brink 2002).

7.CRITICAL RESEARCH GAPS AND FUTURE DIRECTIONS

7.1 Significant Research Deficits

The evidence base for Echinacea purpurea in dermatology still has a lot of gaps, despite significant progress(Gallaher, Gallaher et al. 2006) . The six main categories of research gaps are listed in Table 5 along with a prioritised research agenda(Chevallier 2007).

Table 5: *Comprehensive Research Gap Analysis and Prioritized Research Agenda*

Gap Category	Specific Gap	Priority	Timeline	Study Design	Key Outcomes
Standardization	Marker compound selection	High	1–2 years	In vitro studies	Correlation profiles
Clinical: AD	Confirmatory multi-center trial	High	2–4 years	RCT	SCORAD reduction
Clinical: Acne	Proof-of-concept trial	High	2–3 years	RCT	Lesion counts
Mechanism	Barrier enhancement mechanism	Medium	2–4 years	In vitro	Lipid synthesis
Safety	12-month safety study	High	3–5 years	Open-label	Adverse events
Formulation	Liposomal vs. conventional trial	High	2–4 years	RCT	SCORAD

8.CONCLUSIONS

An emphasis on atopic dermatitis and acne vulgaris, this thorough systematic review has assessed the available data for Echinacea purpurea in dermatological applications(Vargas-Vizuet, Muñoz et al. 2025). Several important conclusions are supported by the synthesis of phytochemical, mechanistic, preclinical, clinical, and formulation data(Juckett 2008).

Principal Findings: With more than 200 identified compounds, Echinacea purpurea has a varied phytochemical profile(Dayal and Nigam). Alkylamides suppress the production of pro-inflammatory cytokines in activated keratinocytes (IL-6: 67.3% reduction; IL-8: 71.8% reduction; $p<0.01$) by acting as selective CB2 receptor agonists (Ki = 85 ± 23 nM)(Upton, Graff et al. 2016). Chicoric acid activates the Nrf2 pathway and has direct antioxidant activity (DPPH IC_{50} = 18.5 ± 2.3 μM)(Percival and Turner 2002). Topical E. purpurea extract significantly lowers local SCORAD scores (mean reduction 7.2 ± 1.8 points greater than comparator, $p<0.01$) and restores epidermal barrier function (ceramide EOS increase 34.2%, $p<0.001$), according to a randomised controlled trial(Geyer and Osorio 2015). Preclinical research shows dual anti-inflammatory (94-96% cytokine inhibition) and antimicrobial (MIC_{90} = 0.5 mg/mL) activity against C. acnes·With sustained release (t½ = 6.2 hours) and improved cytoprotection (89.3% viability vs. 62.1% for free extract, $p<0.01$), liposomal encapsulation achieves 63–75% entrapment efficiency(Walker 1996). Standardisation, clinical trial expansion, mechanistic clarification, long-term safety, formulation optimisation, and comparative effectiveness were found to be the six main research gaps(Draelos 2008).

Concluding Remarks: The successful fusion of traditional knowledge with contemporary scientific methodology is demonstrated by the dermatological revival of Echinacea purpurea(Adams). E. purpurea is positioned for

evidence-based integration into contemporary dermatotherapeutics and regulatory consideration as a botanical drug due to the convergence of mechanistic clarity, clinical validation, and formulation innovation(Jacobs, Reed et al.).

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